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The First RNA Editing Clinical Candidate

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July 12, 2023

Emerging leader in RNA medicines

Multi-modal drug discovery and development platform to address new areas of disease biology
RNA editing, splicing and silencing

Differentiated, clinical-stage RNA medicines pipeline with first-in-class RNA editing programs

Strategic collaborations to expand and advance pipeline (GSK and Takeda)

Multiple pipeline and platform catalysts expected in 2023 and beyond

Well-capitalized with expected cash runway into 2025

GMP manufacturing

Strong and broad IP position[1]

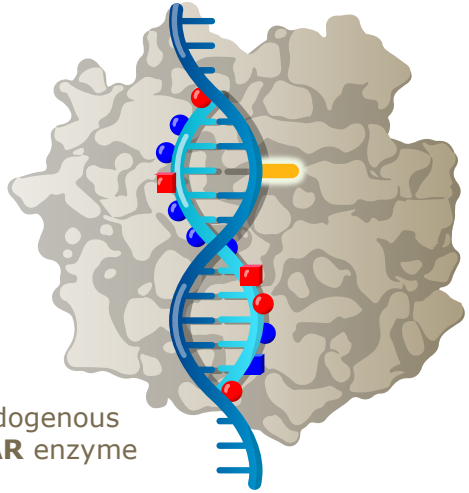
Wave Life Sciences is an RNA medicines company committed to delivering life-changing treatments for people battling devastating diseases

[1]stereopure oligonucleotides and novel backbone chemistry modifications

RNA medicines platform allows matching disease target to therapeutic modality

RNA Base Editing

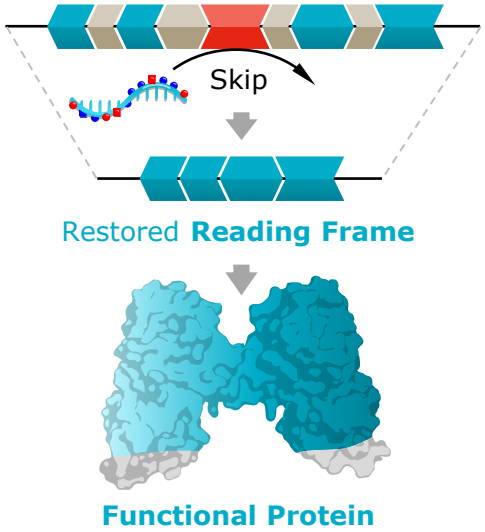
- Efficient editing of RNA bases to **restore** or **modulate** protein production



Endogenous **ADAR** enzyme

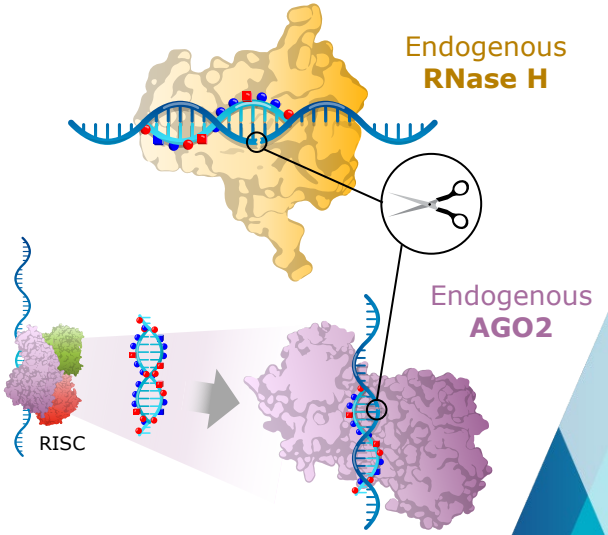
Splicing

- Restore RNA transcripts and **turn on** protein production



Silencing

- Degradation of RNA transcripts to **turn off** protein production



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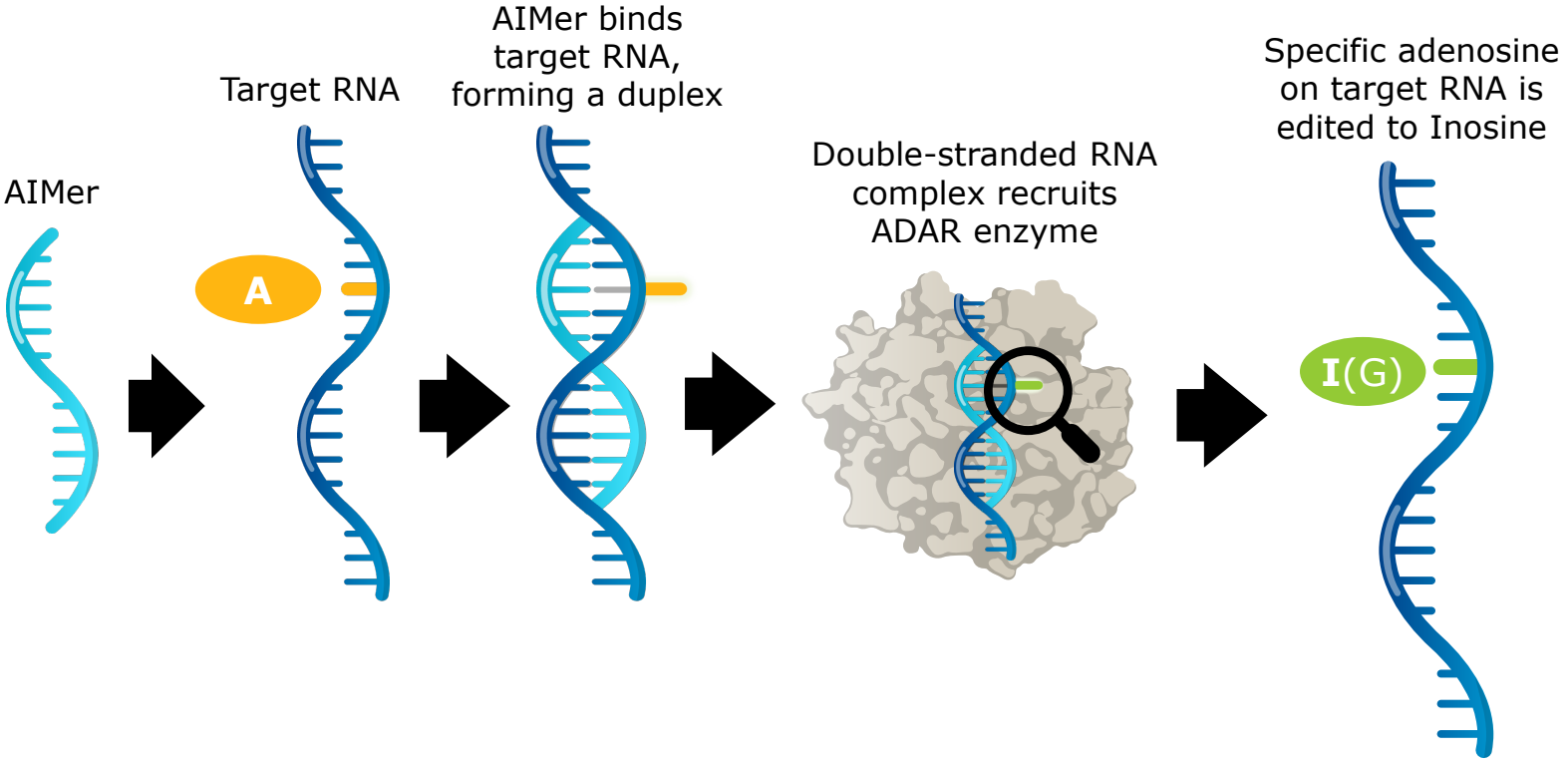
Wave's AIMer platform can edit RNA in a highly specific manner using endogenous protein



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Unlocking therapeutic RNA editing with AIMers: A-to-I editing oligonucleotides

Optimized AIMer design for endogenous transcripts and GalNAc conjugation

nature biotechnology

ARTICLES

https://doi.org/10.1038/s41587-022-01225-1

Check for updates

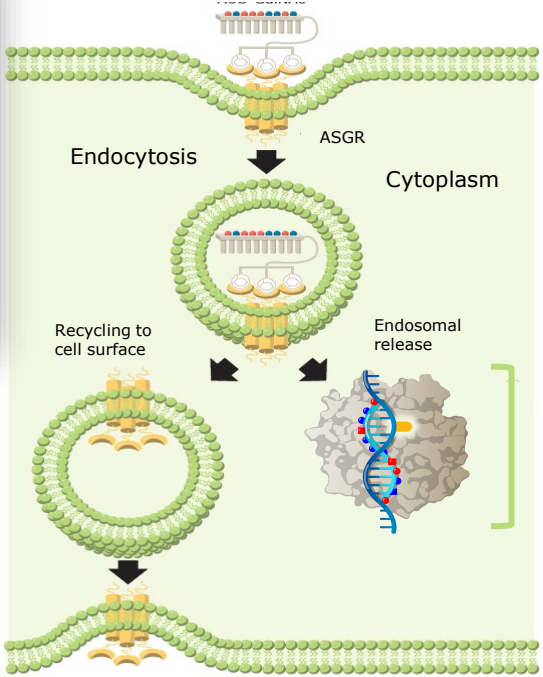
Endogenous ADAR-mediated RNA editing in non-human primates using stereopure chemically modified oligonucleotides

Prashant Monian[1,2], Chikdu Shivalila[1,2], Genliang Lu[1], Mamoru Shimizu[1], David Boulay[1], Karley Bussow[1], Michael Byrne[1], Adam Bezigian[1], Arindom Chatterjee[1], David Chew[1], Jigar Desai[1], Frank Favaloro[1], Jack Godfrey[1], Andrew Hoss[1], Naoki Iwamoto[1], Tomomi Kawamoto[1], Jayakanthan Kumarasamy[1], Anthony Lamattina[1], Amber Lindsey[1], Fangjun Liu[1], Richard Looby[1], Subramanian Marappan[1], Jake Metterville[1], Ronelle Murphy[1], Jeff Rossi[1], Tom Pu[1], Bijay Bhattarai[1], Stephany Standley[1], Snehlata Tripathi[1], Hailin Yang[1], Yuan Yin[1], Hui Yu[1], Cong Zhou[1], Luciano H. Apponi[1], Pachamuthu Kandasamy[1] and Chandra Vargeese[1]✉

Seminal publication demonstrated foundational AIMer designs

Subsequent optimization work has further enhanced pharmacology

GalNAc-mediated uptake



Optimized AIMer design

- ✓ Substrate learnings from biology and structures
- ✓ Applied to oligonucleotides
- ✓ Applied PRISM chemistry

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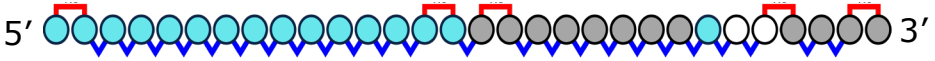
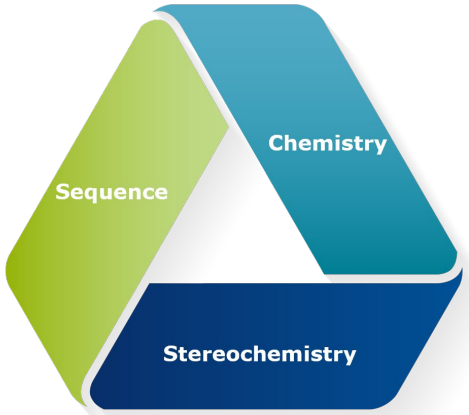
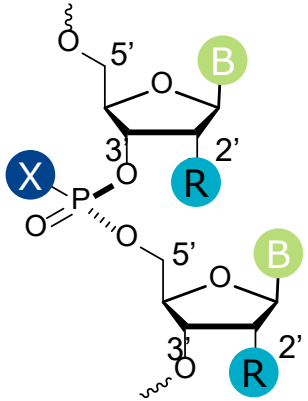
Woolf *et al.*, 1995 *Proc Natl Assoc Sci* 92:8298-8302; Monian *et al.*, 2022 *Nature Biotech* published online Mar 7, 2022 doi: 10.1038.s41587-022-01225-1

Enhancing editing activity of AIMers through application of PRISM chemistry

First Generation AIMer Design





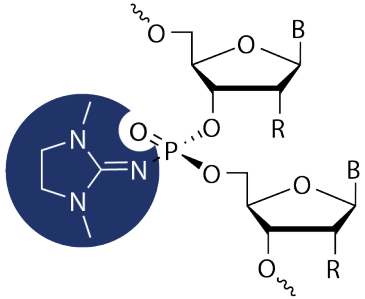


X:
O (Phosphodiester),
S (Phosphorothioate),
N (Phosphoryl guanidine)

B Base

R 2′-ribose modification

X Stereochemistry & backbone modification



Phosphoryl guanidine

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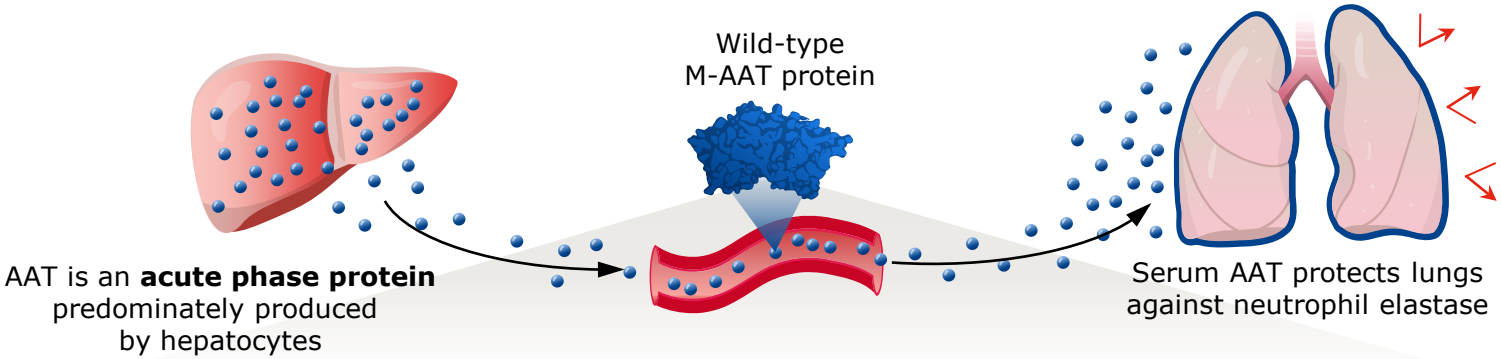
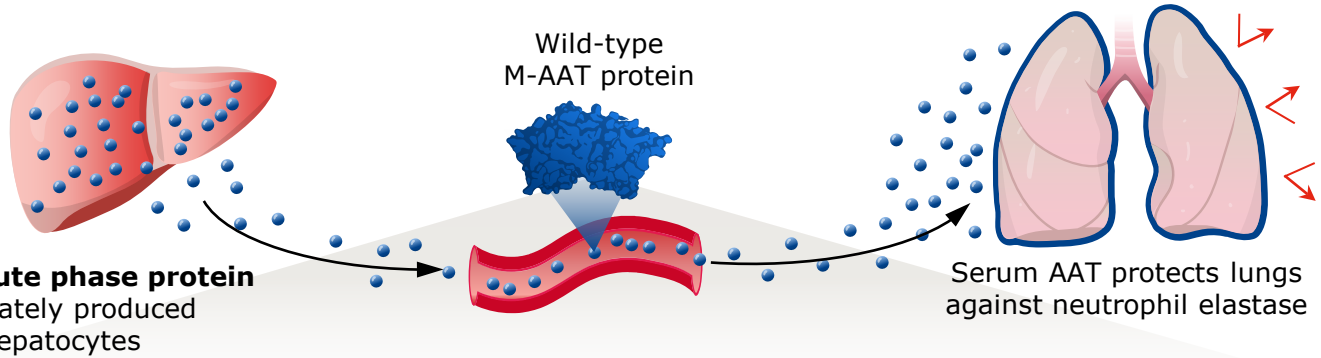
Monian et al., 2022 *Nature Biotechnol* doi: 10.1038/s41587-022-01225-1

SERPINA1 Z mutation: The most common cause of AATD



Strnad *et al.*, 2020 *N Engl J Med* 382:1443-55; Stoller et al., 1993 *Alpha-1 Antitrypsin Deficiency* GeneReviews

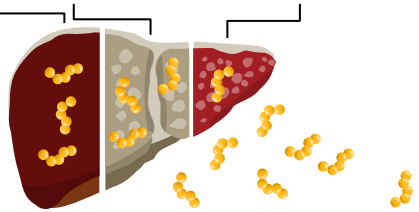
SERPINA1 Z mutation: The most common cause of AATD



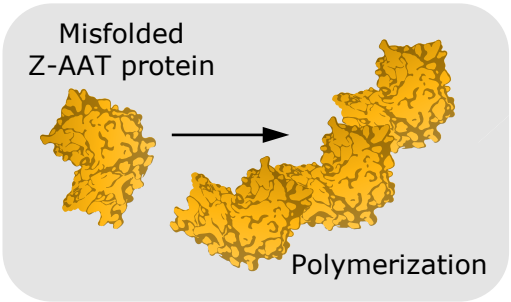
Gain-of-function and loss-of-function disease

Liver Disease

Fibrosis → Cirrhosis → Hepatocellular Carcinoma



E342K mutation causes AAT proteotoxic stress, leading to progressive liver disease



Lung Disease

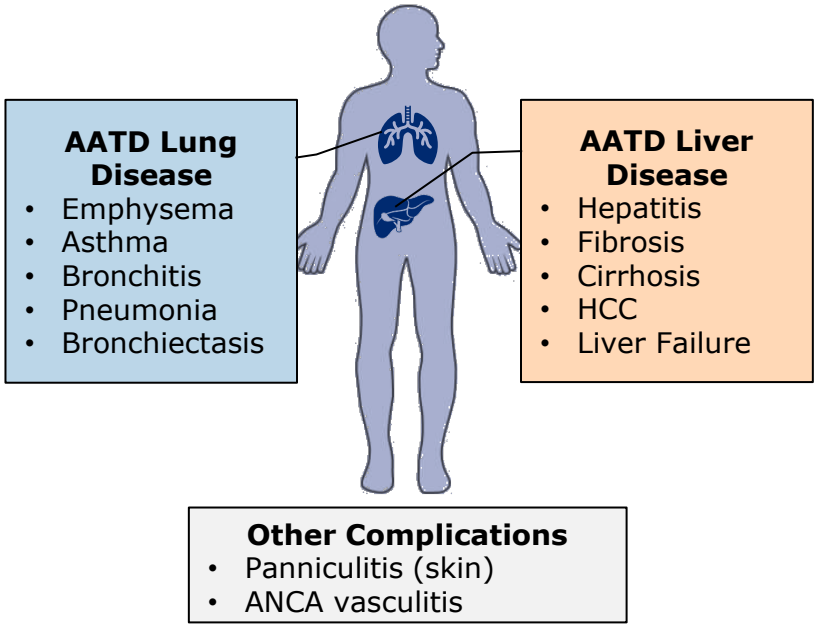
Emphysema Bronchiectasis

Low serum AAT leads to lung disease

Strnad *et al.*, 2020 *N Engl J Med* 382:1443-55; Stoller et al., 1993 *Alpha-1 Antitrypsin Deficiency* GeneReviews

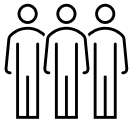
AATD may result in lung and liver disease and has limited treatment options

- ***SERPINA1* Z mutation** (E342K) is most common cause of AATD
- **~200,000 Pi*ZZ patients** in US and Europe[2]
- **Augmentation therapy** is only treatment option for AATD lung disease and requires weekly IV infusions
- **No treatment for AATD liver disease**, other than liver transplant
- Average age of diagnosis of AATD lung disease is **46 years**[3] and average age of adult-onset liver disease is **61 years**[4]
- AATD market today is estimated at **~$1.3B worldwide**[5] despite limitations of current treatment



1. Greene, C.M., *et al.*, 2016 Nat Rev Dis Primers 2, 16051; 2. Blanco *et al.*, 2017 *Int J Chron Obstruct Pulmon Dis* 12:561-69; 3. Strnad, *et al.* 2020 *N Engl J Med* 382:1443-55; 4. Tanash and Piitulainen 2019 *J Gastroenterol* 54:541-548; 5. Evaluate Pharma

Patient insights highlight burden of AATD



> *It's an **invisible disease.** It seems like it tricks you - I look healthy and then I tell someone I can't help them grab something 20 feet away. That's the disconnect.*

> *I used to own a salon and with my lungs going bad so quickly, I had to do away with that…I get **short winded**…I lay around a lot, I'm sick a lot.*

> *It makes it harder for us to travel and go do things, because I have to be home once a week for my infusions. It's definitely an **inconvenience**.*

> *I now have very **high elevated liver enzymes and fatty liver** just in the last year. I get a lot of pain on that side. They believe it is related to AATD.*

> *I have back issues, anytime they do a CAT scan or MRI there is always a notation about fatty liver disease and scarring on my liver. **I know it's there. I know there's a problem.** It's just part of my everyday.*

Engaging patient community to inform clinical development plans

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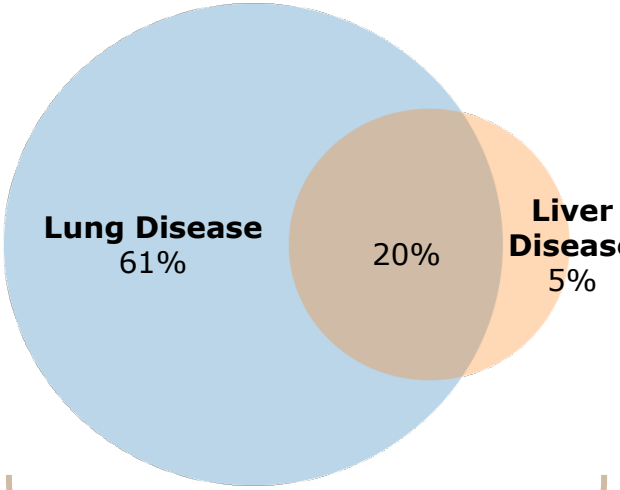
Lumanity AATD Patient Research 2022

AATD landscape is poised to evolve but most approaches focus on lung or liver disease

Selected Therapeutic Strategies in Development for AATD

- Augmentation therapy (Plasma derived, IV) ***[Approved]***
- Recombinant Fc-AAT (IV)
- Inhaled AAT (nebulized)
- Neutrophil elastase inhibitors (oral)

*Frequency of Lung or Liver Disease of Pi*ZZ Patients at Diagnosis**



- RNAi (subcutaneous)
- **WVE-006 (subcutaneous)**
- Gene editing
- Small molecule folding correctors (oral)

**From Alpha One International Registry (n=3,405)*[3] (13% reported no disease at diagnosis)*

1. Rahaghi FF. 2021 Therapeutic Advances in Chronic Disease. 12_suppl.; 2. Fazleen A and Wilkinson T. 2021 ERJ Open Research 7, 00494-2021;
3. McElvaney, *et al.*, 2020 Eur Respir J 55:1902410

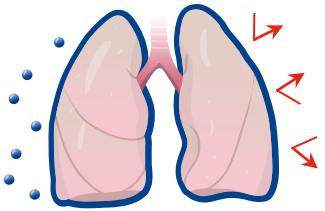
RNA editing is uniquely suited to address the therapeutic goals of AATD

Wave ADAR editing approach potentially addresses all treatment goals:

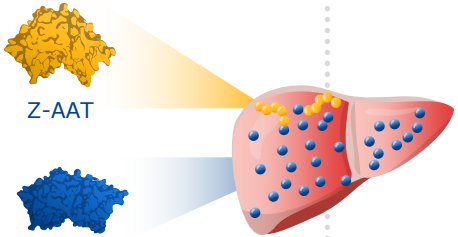
1) Restore circulating, functional wild-type M-AAT

2) Reduce Z-AAT protein aggregation in liver

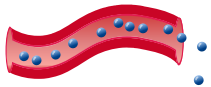
3) Retain M-AAT physiological regulation



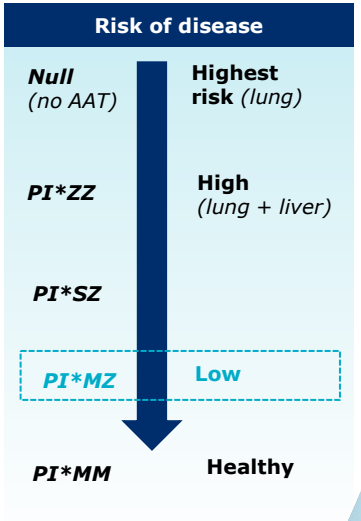
M-AAT reaches lungs to protect from proteases



Wild-type M-AAT protein replaces Z-AAT with RNA correction



M-AAT secretion into bloodstream



Alternative approaches address only a subset of treatment goals:

Standard of care:* *weekly IV protein augmentation *(11μM) addresses only lung manifestations*

siRNA *approaches address only liver disease*

Small molecule *approaches may address the lung and liver but do not restore wild-type M-AAT*

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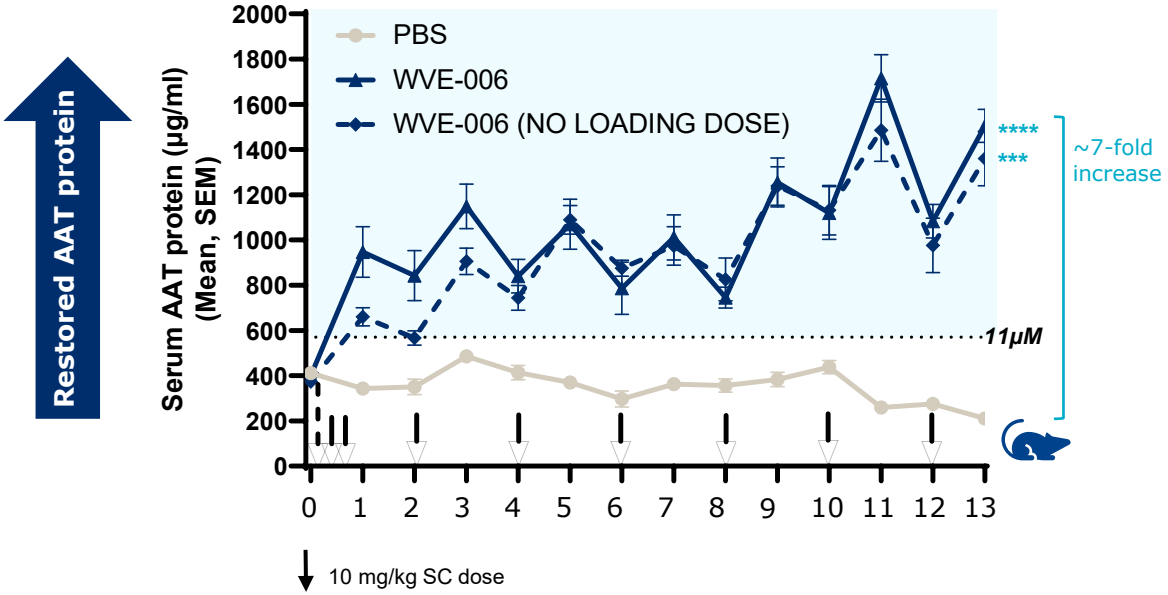
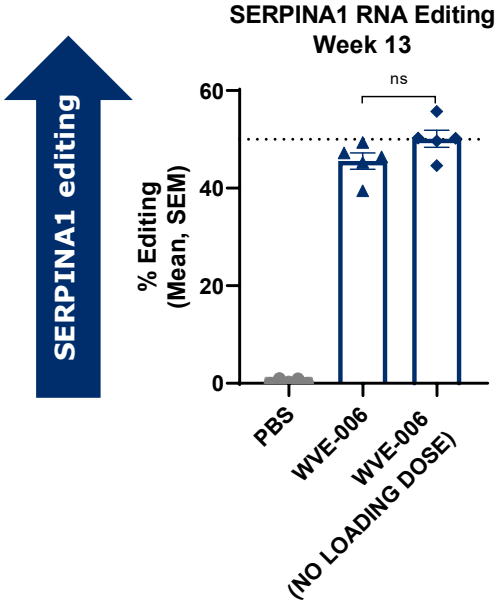
AAT: Alpha-1 antitrypsin Strnad *et al*., 2020 *N Engl J Med* 382:1443-55; Blanco *et al*., 2017 *Int J Chron Obstruct Pulmon Dis* 12:561-69; Remih *et al.,* 2021 *Curr Opin Pharmacol* 59:149-56.

WVE-006 results in circulating AAT protein levels well above established 11 µM threshold *in vivo*

WVE-006 treatment results in serum AAT protein levels >11 uM in AATD mouse model (NSG-PiZ mice)



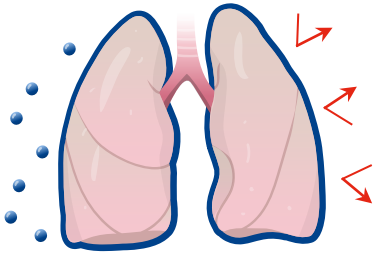
SERPINA1 mRNA editing in liver of AATD mouse model (NSG-PiZ mice, week 13)



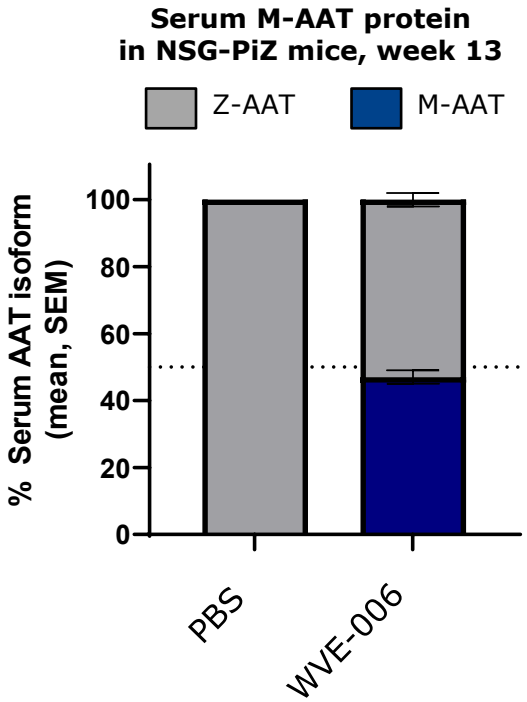
WVE-006 is a GalNAc-conjugated AIMer (A to I(G) RNA base editing oligonucleotide); WVE-006 administered in 7-week old NSG-PiZ mice (n=5 per group); Left: Total serum AAT protein quantified by ELISA; Stats: 2-way ANOVA with Dunnett post-hoc comparison to PBS ****<0.0001, *** <0.001; Right: Liver biopsies collected at week 13 (one week after last dose) and SERPINA1 editing was quantified by Sanger sequencing; Stats: 1-way ANOVA with Tukey post-hoc comparisons between all groups (only difference between dose groups shown) ns=non-significant

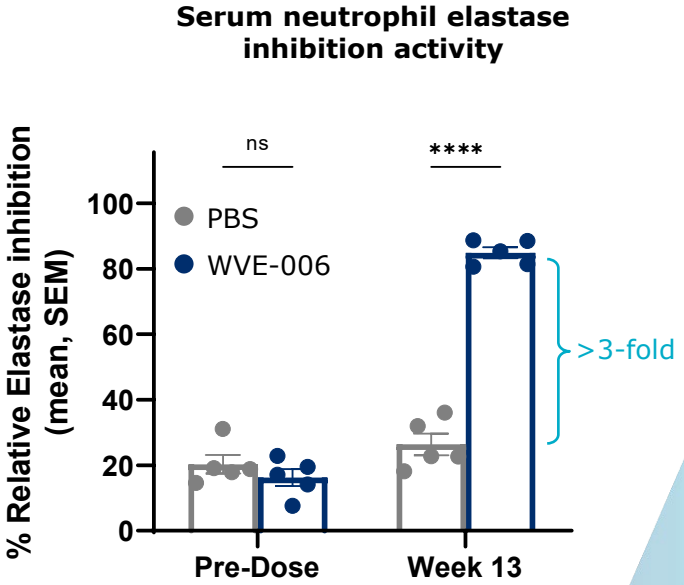
WVE-006 restores serum M-AAT protein in mice, increases serum neutrophil elastase inhibition

Correction of loss-of-function phenotypes



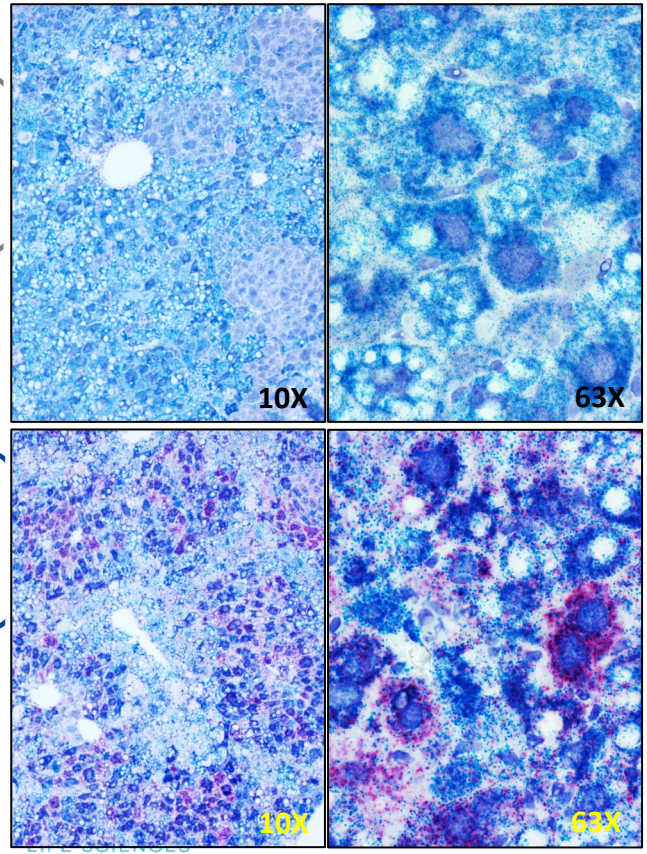
Restored M-AAT reaches lungs to protect from proteases



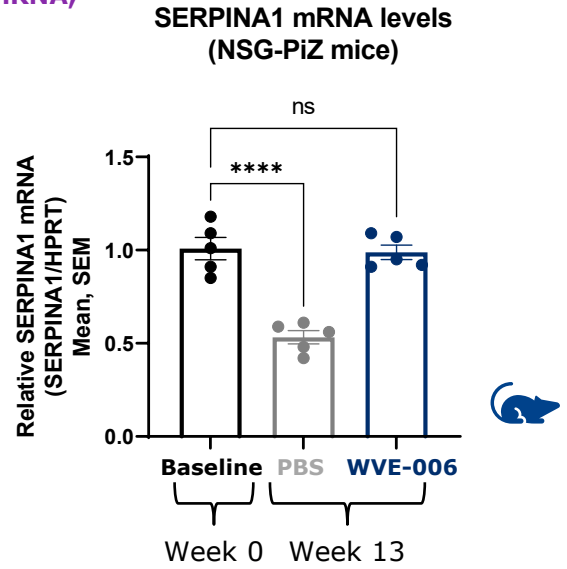


GalNAc-conjugated AIMers administered in 7-week old NSG-PiZ mice (n=5 per group). Proportion of AAT protein in serum measured by mass spec, total AAT protein quantified by ELISA. Serum collected from mice was tested for ability to inhibit fixed concentration of neutrophil elastase in an *in vitro* reaction. Stats: 2-way ANOVA with Bonferroni post-hoc for comparisons between PBS and WVE-006

RNA editing preserves expression of *SERPINA1* transgene in liver of treated mice



Mutant mRNA;
***Wild-type* (edited) mRNA;**
Nucleus

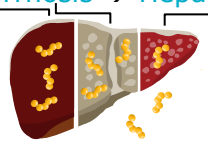


GalNAc-conjugated AIMers administered in 7-week old NSG-PiZ mice (n=5 per group). mRNA expression quantified by qPCR. Stats: 1-way ANOVA with Dunnet post-hoc test for multiple comparisons

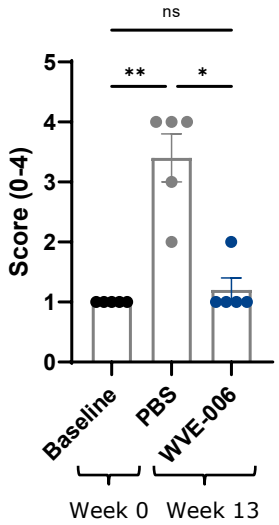
WVE-006 decreases lobular inflammation and PAS-D globule size, prevents increase in hepatocyte turnover

Correction of gain-of-function liver phenotypes

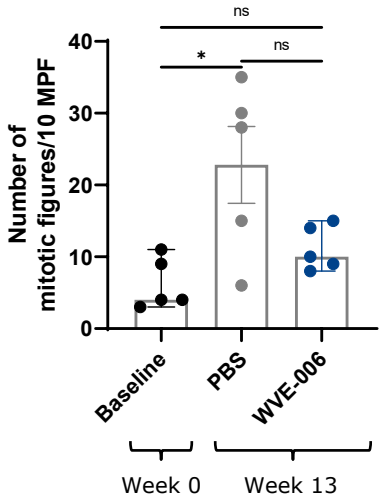
Fibrosis → Cirrhosis → Hepatocellular Carcinoma



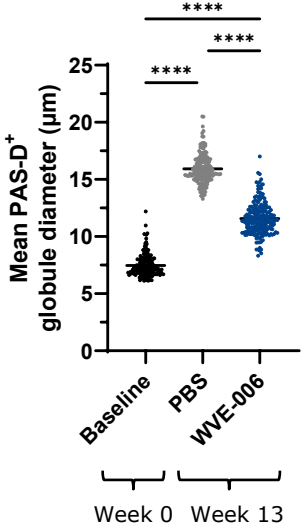
Lobular inflammation
(NSG PiZ mice, week 13)



Mitoses
(NSG PiZ mice, week 13)



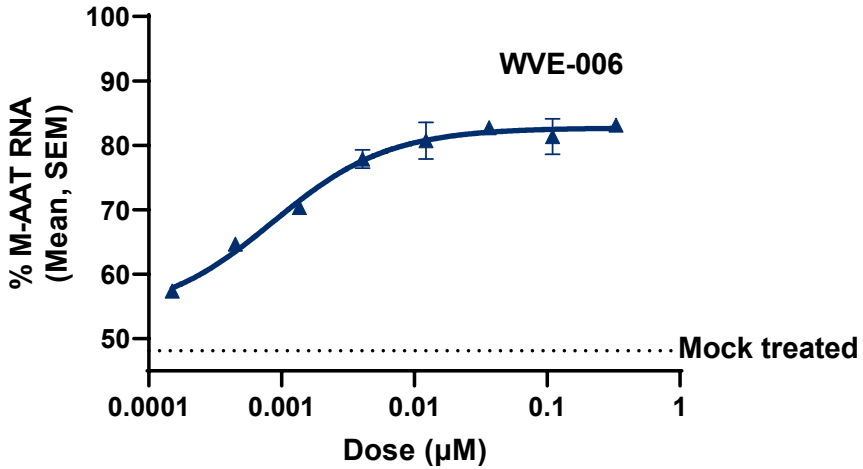
PAS-D-positive globule size
(NSG PiZ mice, week 13)



Left (Lobular inflammation) and Middle (Mitoses): Scatter plot showing inflammation grade or mitoses score. Each circle represents an individual mouse, (Mean ± SEM); Right (PAS-D Globule Size): 40 largest globules in each of 5 mice were measured. Each circle represents a single PAS-D globule, (Mean ± SEM). Baseline: week 0 (7 weeks old); Treated week 13 (20 weeks old); Stats: Kruskal-Wallis followed by Dunn's test

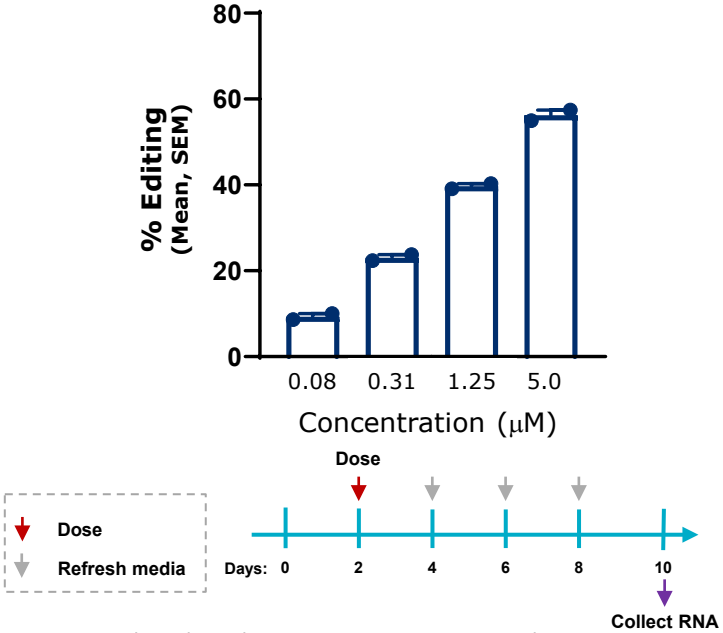
WVE-006 supports dose-dependent RNA editing in human preclinical model systems

Efficient SERPINA1 editing in donor-derived primary human hepatocytes with WVE-006 (MZ genotype)



Note: Due to MZ genotype, Y-axis ranges from ~50-100%

Editing in iPSC-derived human hepatocytes with WVE-006 (ZZ genotype)

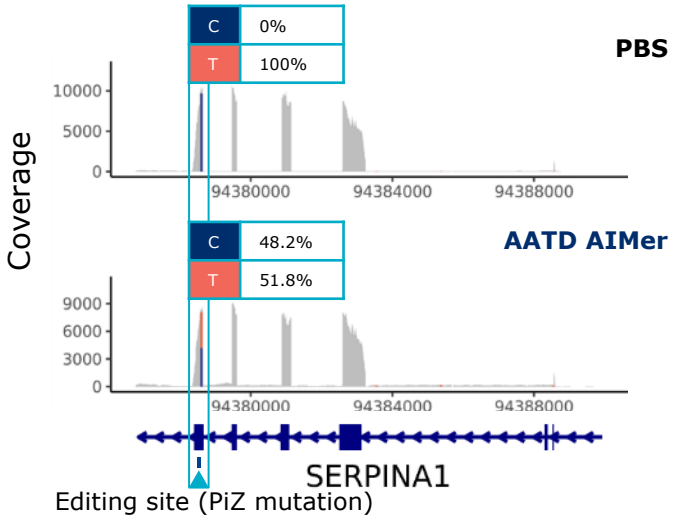


Primary human hepatocytes with MZ (left) or ZZ (right) genotype treated with WVE-006 at the indicated concentrations. Percentage editing was determined by Sanger sequencing.

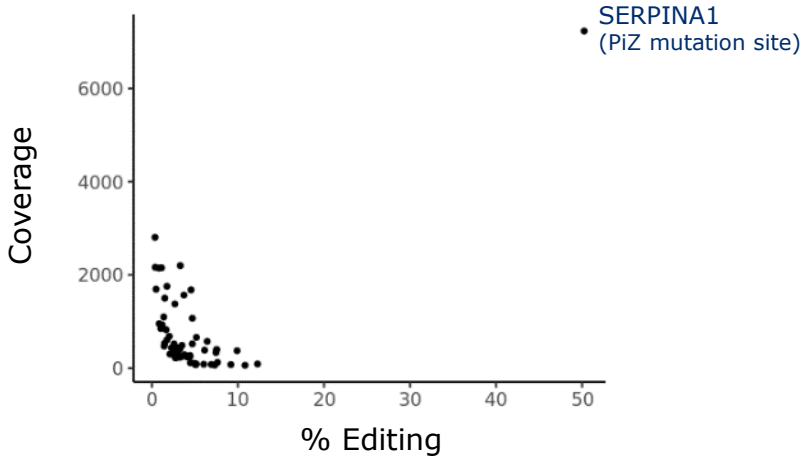
AIMer-directed editing is highly specific in mice

No bystander editing observed on SERPINA1 transcript

RNA editing only detected at PiZ mutation site in SERPINA1 transcript
(mouse liver)



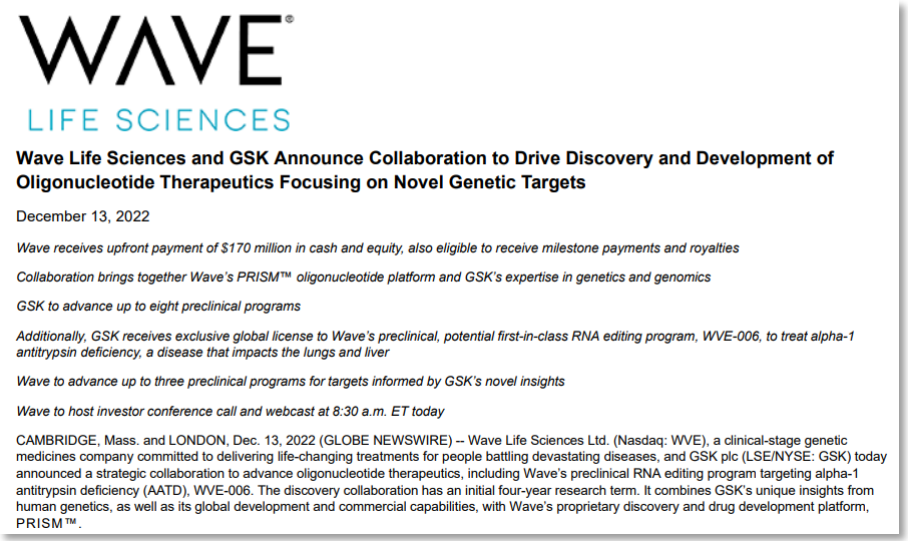
RNA editing across transcriptome
(mouse liver)



Dose 3x10 mg/kg (days 0, 2, 4) SC with AATD AIMer (SA1 – 4). Liver biopsies day 7. RNA-seq to quantify on-target SERPINA1 editing, to quantify off-target editing reads mapped to entire mouse genome; plotted circles represent sites with LOD>3 (N=4), SERPINA1 edit site is indicated

WVE-006 is part of Wave's collaboration with GSK

Collaboration set up to maximize global commercial potential of WVE-006 in AATD



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Wave Life Sciences and GSK Announce Collaboration to Drive Discovery and Development of Oligonucleotide Therapeutics Focusing on Novel Genetic Targets

December 13, 2022

Wave receives upfront payment of $170 million in cash and equity, also eligible to receive milestone payments and royalties

Collaboration brings together Wave's PRISM™ oligonucleotide platform and GSK's expertise in genetics and genomics

GSK to advance up to eight preclinical programs

Additionally, GSK receives exclusive global license to Wave's preclinical, potential first-in-class RNA editing program, WVE-006, to treat alpha-1 antitrypsin deficiency, a disease that impacts the lungs and liver

Wave to advance up to three preclinical programs for targets informed by GSK's novel insights

Wave to host investor conference call and webcast at 8:30 a.m. ET today

CAMBRIDGE, Mass. and LONDON, Dec. 13, 2022 (GLOBE NEWSWIRE) -- Wave Life Sciences Ltd. (Nasdaq: WVE), a clinical-stage genetic medicines company committed to delivering life-changing treatments for people battling devastating diseases, and GSK plc (LSE/NYSE: GSK) today announced a strategic collaboration to advance oligonucleotide therapeutics, including Wave's preclinical RNA editing program targeting alpha-1 antitrypsin deficiency (AATD), WVE-006. The discovery collaboration has an initial four-year research term. It combines GSK's unique insights from human genetics, as well as its global development and commercial capabilities, with Wave's proprietary discovery and drug development platform, PRISM™.

- ✓ Leverages GSK expertise in:
  - Respiratory outcomes studies
  - Global development
  - Global commercialization
- ✓ Transfers to GSK after Wave completes first-in-patient study
- ✓ Initial CTA submissions expected in 2H 2023

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Clinical validation of WVE-006 would unlock and derisk additional therapeutic applications of AIMers

WVE-006 for AATD (GalNAc-AIMer)

Poised to be first RNA editing candidate to enter the clinic

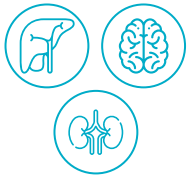
Restoration of M-AAT protein validates:

- ✓ RNA editing in AATD
- ✓ RNA editing as new therapeutic modality

Restore or correct protein function

Expanding in multiple therapeutic applications beyond precise correction of single base mutations, including **upregulation** and **modulation of protein interactions**

Hepatic
CNS
Renal



Monogenic rare diseases

Prevalent diseases

Benefits of AIMers as a modality:

- ✓ Efficient ADAR recruitment
- ✓ Stability, durability
- ✓ Ease of delivery (GalNAc, free uptake)
- ✓ Low risk of off-target or bystander edits
- ✓ Maintains integrity of the genome

Anticipate investor event in 3Q 2023 during which Wave will demonstrate how it is continuing to extend its leadership in RNA editing and share preclinical data

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AIMer: A-to-I(G) RNA base editing oligonucleotides; AATD: Alpha-1 antitrypsin deficiency; AAT: Alpha-1 antitrypsin

Conclusions

- AATD represents significant commercial opportunity; a single therapeutic that can correct underlying disease pathology and treat liver and lung manifestations has potential to be best-in-class
- WVE-006 is intended to correct homozygous "*ZZ*" mutations to an "*MZ*" heterozygous state
- WVE-006 led to a 7-fold increase in serum AAT protein levels in AATD mouse model and is well above 11 μM - the anticipated therapeutic threshold[1]
- Restored serum M-AAT is functional and may protect lungs from damage; repeat dosing with WVE-006 improved several markers of liver disease in mice
- CTA submissions for first-in-human study expected in 2H 2023
- WVE-006 licensed to GSK in December 2022 as part of strategic collaboration to maximize commercial potential of WVE-006
- Clinical validation of WVE-006 would unlock and derisk additional therapeutic applications of AIMers

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[1]Brantly et al., 2018 *Chronic Obstr Pulm Dis*

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Questions?